GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

**Week of February 1 - 5, 2021**

**SPOTLIGHT: SSRIs Improve Neurologic Function during Post-Stroke Recovery**

- Pediatric Respiratory Tract Infections: How long is too long?
- Exercise in the Elderly: Could long-term exercise reduce adverse events?
- Treating Croup with Dexamethasone
- Survival of the FITest: Repeated Fecal Immunochemical Test as a Screening Program for Colorectal Cancer

# Selective Serotonin Reuptake Inhibitors Improve Neurologic Function during Post-Stroke Recovery

**Early Selective Serotonin Reuptake Inhibitors for Recovery after Stroke: A Meta-Analysis and Trial Sequential Analysis**
Si-Chun G, Chang-De W. Early Selective Serotonin Reuptake Inhibitors for Recovery after Stroke: A Meta-Analysis and Trial Sequential Analysis. *Journal of Stroke and Cerebrovascular Diseases.* 2018; 27(5):1178–1189.



**KEY TAKEAWAY:** In adults recovering from a stroke, early treatment with a selective serotonin reuptake inhibitor (SSRI) improves neurologic function.

**STUDY DESIGN:** Meta-Analysis of 8 RCTs; N=1549

**LEVEL OF EVIDENCE:** STEP 2 (downgraded for significant heterogeneity)

**BRIEF BACKGROUND INFORMATION:** Stroke is a leading cause of permanent disability. The risks and benefits of early (≤30 days from stroke onset) SSRI treatment for improvement of disability recovery is not well understood and further analysis is needed.

**PATIENTS:** Non-depressed adults, age 18 years or older, who had a recent stroke within the last month with confirmatory brain imaging.

**INTERVENTION:** SSRI treatment within 1 month of stroke onset

**CONTROL:** Routine care with placebo treatment

**OUTCOME:** Primary outcome was the change in National Institutes of Health Stroke Scale (NIHSS) score while on an SSRI vs Placebo. A decrease in score would potentially show benefit. Secondary outcomes included change in Barthel Index, functional independence based on Rankin Score, incidence of depression and adverse events. The Barthel index is a measure of performance of activities of daily living based on a scale of 0–100, the higher number being better. The Rankin Scale measures functional outcome on a 7-point scale, 0 being no symptoms to 6 being death.

**METHODS (BRIEF DESCRIPTION):** Authors performed an electronic literature search for trials meeting the PICO criteria.

- A total of 2091 studies were identified and 33 were reviewed. 8 studies met the inclusion criteria.
- Trials were excluded that were of studies still ongoing, were not RCTs, did not meet the inclusion criteria, were duplicate studies, and did not contain keywords in the title or abstract.
- 8 studies met the inclusion criteria: 1 RCT for 20 mg citalopram, 1 RCT for 5mg and 10 mg escitalopram, 2 RCTs for 50mg sertraline, and 4 RCTs for 20 mg fluoxetine
- 6 trials were included to assess the primary outcome, 4 trials included to assess secondary outcomes
- Treatment was initiated within 7–28 days of stroke onset and continued for 2–12 months
- Just over 1/3 of participants were female; mean age was 63 years
- NIHSS score and Barthel index outcomes were compared to baseline data; functional independence, incidence of depression and adverse events were measured as present or absent

**INTERVENTION (# IN THE GROUP):** 849
**COMPARISON (# IN THE GROUP):** 735

**FOLLOW UP PERIOD:** Range: 8 weeks-1 year

**RESULTS:**

**Primary outcome:**

- Patients receiving SSRI treatment within 30 days of stroke onset showed a more significant improvement in NIHSS score from baseline vs placebo (WMD, 0.82; 95% CI, 0.31–1.33, P=.002)

**Secondary outcomes:**

- Patients receiving early SSRI treatment showed significantly improved scores in SSRI groups vs placebo with the Barthel Index (WMD, 5.32; 95% CI, 1.65–8.99, P=.005); 2 trials were included
- Patients in the early SSRI group had significantly higher functional independence vs placebo based on Rankin Scale (95% CI, 1.82–3.55, P<.0001); 3 trials were included
- Patients receiving early SSRI treatment showed no significant difference of incidence of depression vs placebo (95% CI, 0.41–1.23, P=.52)
- Patients receiving early SSRI treatment did not have a significant difference vs placebo for incidence of diarrhea, insomnia, hepatic enzyme disorders, seizure, and intracranial hematoma

**LIMITATIONS:**

- Although the analysis supports early use of SSRIs, there is no evidence as to which SSRI is more effective, nor which dose or duration of therapy is most effective.
- Some of the secondary outcomes had a smaller number of studies included.
- Most trials included shorter follow up, making conclusions about long-term outcomes limited.
- Many of the trials did not include adults over the age of 80 or patients with severe post-stroke disability.

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# Pediatric Respiratory Tract Infections: How long is too long?

**Respiratory Tract Infections in Children in the Community**

Hay AD, Anderson E, Ingle S, et al. Respiratory tract infections in children in the community: prospective online inception cohort study. *Ann Fam Med*. 2019; 17(1):14–22.



**KEY TAKEAWAY:** In children, respiratory tract infection symptoms can last up to three weeks. Parents may pursue primary care assistance in at least 1 in 12 illnesses.

**STUDY DESIGN:** Community-based, online, prospective inception, cohort study

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Proper antibiotic stewardship and treatment of respiratory tract infections (RTI) requires an accurate understanding of illness duration and self-healing. Current studies describe RTI characteristics based on care-seeking patients; therefore, current data sets are incapable of quantifying the total number of people falling ill and the proportion seeking care. To assist providers and policy makers, this study seeks to demonstrate the feasibility of online data collection for these two metrics.

**PATIENTS:** Children 3 months to 15 years old from general physician practices within 10 miles of Bristol, United Kingdom without immune compromising conditions or terminal illnesses

**INTERVENTION:** Daily parent record of RTI severity and duration online. Beyond 21 days of illness, symptoms were recorded weekly.

**CONTROL:** No comparison group

**OUTCOME:** The primary outcome included the duration of RTI symptoms. Secondary outcomes included the number of care consultations, antibiotic prescriptions offered, days out of school or nursery, parental days off of work, and the amount of money spent on medications.

**METHODS (BRIEF DESCRIPTION):** Families were recruited from general practices within 10 miles of Bristol, United Kingdom by mailed invitation. Consenting parents received weekly emails/texts questioning if their child had new RTI symptoms. For a negative response, further action was not required. For a positive response, parents posted online the child's daily symptoms and severity using the Likert scale. Beyond 21 days of symptoms, entries were weekly. Quantification of the days of school/nursey missed, days of work missed, and medication costs occurred weekly. Provider notes were utilized to count the number of antibiotic prescriptions and consultations, including telephone calls and emergency department visits.

**INTERVENTION (# IN THE GROUP):** 10,310 children invited, 485 enrolled in online cohort, 259 children with parent-reported RTI episodes

**COMPARISON (# IN THE GROUP):** No comparison group

**FOLLOW UP PERIOD:** Initial paperwork mailings to parents/caregivers were staggered between February 25, 2016 and July 1, 2016. Data was collected on new symptoms presenting before July 31, 2016 through symptom resolution.

**RESULTS:**

- Primary outcome: Median RTI duration was 9 days. It took 23 days for 90% (95% CI, 85%–94%) of children to recover.
- Median symptom duration was longer:
  - In children with primary care consultations vs. those without consultations (9 days vs. 6 days, p=0.06)
  - In children <3 years old vs. >3 years old (11 days vs. 7 days, p<0.01)
  - In children with lower RTI symptoms vs. those with exclusively upper RTI symptoms (12 days vs. 8 days, p<0.001)
- 16 of the first 197 RTI episodes resulted in primary care consultations (8.1%, 95% CI, 4.7%–12.8%). 3 of these visits resulted in an amoxicillin prescription.
- 60 of 188 parents reported paying for new medications for their child's illness (31.9%, 95% CI, 25.2%–38.6%). The mean cost was $8.12.

**LIMITATIONS:**

- There was a low response rate to the initial paper mailer.
- Responding parents/caregivers trended towards younger children and less socioeconomic diversity.
- Responding families had higher than average medical knowledge than the general population with 20% of parents reporting medical or nursing training.
- There was a short duration of observation.
- Observation occurred during summer likely resulting in the inclusion of allergy symptoms.
- The effect of maternal socioeconomic deprivation and education on symptom duration and consultation could not be determined due to insufficient sample size.
- Symptom duration could have been overestimated by more participation of younger children with longer illness durations and the inclusion of all respiratory symptoms. Symptom duration could have been underestimated by parents prematurely discontinuing symptom diary entries.
- The email/text system did not distinguish between unresponsive parents and parents reporting no new symptoms.
- Previous research suggests less-affluent families are more likely to seek primary care consultants. Therefore, the consultation rate may have been underestimated in this study.

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# Exercise in the Elderly: Could long-term exercise reduce the risk of falls, fractures, hospitalizations, and mortality?

**Association of Long-term Exercise Training with Risk of Falls, Fractures, Hospitalizations, and Mortality in Older Adults a Systematic Review and Meta-analysis**

de Souto Barreto P, Rolland Y, Vellas B, et al. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults. A systematic review and meta-analysis. *JAMA Intern Med*. 2019; 179(3):394–405.



**KEY TAKEAWAY:** Long-term exercise (>1 year) is associated with a statistically significant reduction in falls and injurious falls. Exercise did not significantly diminish the risk of multiple falls, hospitalization, mortality, and fractures.

**STUDY DESIGN:** Systematic review of 46 (22709 participants) long-term randomized clinical trials (RCT's) with a preplanned meta-analysis of 40 (21868 participants) RCT's

**LEVEL OF EVIDENCE:** STEP 1

**BRIEF BACKGROUND INFORMATION:** Exercise training is an important intervention for health outcomes, leading to benefits in the body and mind. Despite our understanding of these processes, there are gaps in the research associating exercise and the risk of developing adverse outcomes. The recent LIFE study provided an unexpected outcome, demonstrating increases in hospitalization and mortality among exercisers compared with controls, raising doubts about safety of exercise for older adults. Additionally, previous studies have provided mixed results about the effect of exercise in preventing fractures.

**PATIENTS:** Adults 60 years or older at baseline or a mean population age 60 years or older

**INTERVENTION:** Long term exercise training (> 1 year) performed at any frequency, intensity, and session duration

**CONTROL:** No intervention

**OUTCOME:** Six outcomes were measured including: mortality, hospitalization, people who fell at least once, people who fell multiple times, people who suffered injuries from falling, and people who sustained a fracture from falling

**METHODS (BRIEF DESCRIPTION):** The authors used PRISMA guidelines and performed electronic searches within PubMed, Cochrane Central Register of Controlled Trials, SportDiscus, PsychInfo, and Ageline. The authors used the following inclusion criteria:

- RCT design with exercise length of 1 year or longer
- The study compared the effects of at least 1 exercise intervention against a comparator group.
- All kinds of exercise intervention structure were eligible and unsupervised exercises was only included when a personalized exercise plan was used.
- Participants were 60 years or older at baseline or the mean population age was 60 years or older.

Cochrane Collaboration tool was used to evaluate the risk of bias.

**INTERVENTION (# IN THE GROUP):**

- Mortality: 5677
- Hospitalization: 2822
- Falls: 2207
- Multiple Falls: 1526
- Injurious Falls: 2192
- Fractures: 4138

**COMPARISON (# IN THE GROUP):**

- Mortality: 5764
- Hospitalization: 2817
- Falls: 2213
- Multiple Falls: 1532
- Injurious Falls: 2289
- Fractures: 4272

**FOLLOW UP PERIOD:** Varied per study. At least 1 year

**RESULTS:**

- Exercise is associated with a modest decrease in the risk in falls (n=20 RCTs; RR 0.88, 95% CI 0.79–0.98) and injurious falls (n=9 RTCs; RR 0.74, 95% CI 0.62–0.88) and tended to reduce the risk of fractures, but not significantly (n=19 RTCs, RR 0.84, 95% CI 0.71–1.0, P=0.05).
- Exercise did not diminish the risk of multiple falls (13 RTC's), hospitalization (12 RTC's), and mortality (29 RTC's).
- Meta-regressions on mortality and falls suggest that 2–3 times per week would be the optimal exercise frequency.

**LIMITATIONS:**

- Several studies included did not clearly report exercise adherence, which made it challenging to determine the exercise volume of the participants.
- The 1-year length was an arbitrary way to determine long-term exercise. The authors may have lost important studies that employed shorter follow-ups.
- Multiplicity of the analysis performed may have increased the chance for a type I error
- The authors were unable to perform strict subgroup analysis of study population due to the small number of studies for each outcome. They attempted to reduce this bias by performing broader subgroup analysis for populations with and without disease-specific profiles.

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# Treating Croup with Dexamethasone, Low Dose Dexamethasone, or Prednisolone: The Comparison

**Prednisolone versus Dexamethasone for Croup: a Randomized Controlled Trial**

Parker CM and Cooper MN. Prednisolone versus Dexamethasone for Croup: a Randomized Controlled Trial. *Pediatrics.* 2019; 144(3):e20183772



**KEY TAKEAWAY:** Prednisolone, low-dose dexamethasone, and standard-dose dexamethasone are all effective options to treat children with croup.

**STUDY DESIGN:** Multisite, prospective, double-blind, noninferiority randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Dexamethasone 0.6 mg/kg is the gold standard treatment for croup. Although widely used in many medical centers worldwide, dexamethasone 0.15 mg/kg or prednisolone 1mg/kg are not been well studied.

**PATIENTS:** Children age > 6 months (mean age 30 months) with a maximum weight of 20 kg with croup

**INTERVENTION:** Low-dose dexamethasone 0.15 mg/kg or prednisolone 1 mg/kg

**CONTROL:** Dexamethasone 0.6 mg/kg

**OUTCOME:**

- Serial Westley Croup Scores (WCS) ranging from 0–17 based on stridor, retractions, air entry, cyanosis, and level of consciousness. A higher WCS score corresponded to a sicker patient.
- Unscheduled medical return to ED during the 7 days after treatment, as determined by telephone call within 4 weeks after discharge or by search of the electronic medical record if caregiver could not be reached via telephone.

**METHODS (BRIEF DESCRIPTION):** Prospective double-blind randomized controlled study at two pediatric Emergency Departments in Perth, West Australia. Participants were randomly assigned to receive one of three treatment options: 1) 0.6 mg/kg dexamethasone, 2) low-dose 0.15 mg/kg dexamethasone, or 3) prednisolone 1 mg/kg. Inclusion criteria were age greater than 6 months, maximum weight of 20 kg, and clinical diagnosis of croup. Westley Croup Scores were measured at baseline and hourly for up to 6 hours after treatment and again at 12 hours if patient had not yet been discharged. Re-attendance rate within 7 days was assessed via telephone call with caregivers 4 weeks after discharge or via electronic medical record review.

Noninferiority was defined as the upper bound of the 2-sided 95% confidence interval for the reduction of WCS not exceeding 0.5 for the intervention group relative to the standard treatment group.

**INTERVENTION (# IN THE GROUP):** 410 assigned to dexamethasone 0.15 mg/kg; 411 assigned to prednisolone 1 mg/kg

**COMPARISON (# IN THE GROUP):** 410 assigned to dexamethasone 0.6 mg/kg

**FOLLOW UP PERIOD:** 4 weeks

**RESULTS:**

- At 1 hour, there was no statistically significant difference in WCS relative to standard-dose dexamethasone when adjusted for age, study center, and baseline WCS:
  - low-dose dexamethasone: 0.03 (95% CI -0.09 to 0.15)
  - prednisolone: 0.05 (95% CI -0.07 to 0.17)
- Even at 2 and 3 hours, the difference in WCS for both low-dose dexamethasone and prednisolone relative to standard-dose dexamethasone remained below the non-inferiority margin of 0.5.
- There was no statistically significant difference relative to standard-dose dexamethasone in unscheduled re-attendance rate with general practitioner or Emergency Department:
  - dexamethasone 17.8%
  - low-dose dexamethasone: 19.5% (p=0.59)
  - prednisolone 21.7% (p=0.19)

**LIMITATIONS:**

- Similar geographical region and patient demographic
- Only 1 in 7 patients with croup were enrolled. Since the authors did not record the number of participants screened for inclusion, it is unclear whether the children with croup not enrolled in the study were due to lapses in screening or parental refusal.
- Only about 70% of enrollees were reached by telephone for follow-up survey

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# Survival of the FITest: Repeated Fecal Immunochemical Test as a Reliable Screening Program for Colorectal Cancer

**Long-term Performance of Colorectal Cancer Screening Programmes Based on the Faecal Immunochemical Test**

Zorzi M, Hassan C, Capodaglio G, et al. Long-term Performance of Colorectal Cancer Screening Programmes Based on the Faecal Immunochemical Test. *Gut*. 2018; 67(12):2124–2130.



**KEY TAKEAWAY:** At least five rounds of repeated fecal immunochemical tests (FITs) are comparable to colonoscopy given the similar detection rates and sensitivity, as well as higher PPV.
**STUDY DESIGN:** Retrospective Cohort Study
**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Colonoscopy has high sensitivity for colorectal cancer and advanced adenoma but is expensive and invasive. FIT may reduce the incidence of CRC, however more data is needed on the long-term performance of FITs to compare sensitivity to colonoscopy. FIT is less invasive and expensive and, therefore, may be a preferable patient-centered approach for CRC detection.
**PATIENTS:** Men and women between the ages of 50 to 69 years old from the Veneto Region of Italy
**INTERVENTION:** Biennial FIT for participants who continuously tested FIT negative throughout the 12-year study period, and appropriate use of colonoscopy resources as needed for those who tested FIT positive
**CONTROL:** None
**OUTCOME:** The primary outcomes were positive predictive value, cumulative sensitivity, and the detection rate of colorectal cancer and advanced adenoma using repeated fecal immunochemical tests

**METHODS (BRIEF DESCRIPTION):** Participants completed a FIT test every 2 years during the study period (2002–2015). Participants were excluded if they missed a screening at any point. If a participant's FIT returned positive proper standard of care with follow-up colonoscopy was provided. If the FIT was false positive, participants were invited back in 5 years. Each round was compared using Pearson's correlations coefficient and Snedecor's F for homogeneity of proportions. Kaplan-Meier method was used to determine cumulative FIT positivity and detection rates for advanced adenoma and CRC. Finally, a multivariable analysis was used to evaluate gender and age trends for each indicator.

**INTERVENTION (# IN THE GROUP):** 123,347
**COMPARISON (# IN THE GROUP):** None in this study, but historic comparisons were referenced

**FOLLOW UP PERIOD:** 12 years

**RESULTS:**

- PPV of FIT positivity for CRC and advanced adenoma was highest in the first round at 36.9% and dropped in subsequent screenings to 20%, likely due to neoplasms being identified in the first round.
- Cumulative CRC detection rate was 8.5% (95% CI 7.8–9.2) and advanced adenoma detection rate was 58.9% (95% CI 56.9–61.0). Higher rates were detected with men and older age (60–64 years old).
- FIT positivity rate was 4.1% from all screening rounds. The cumulative FIT positivity rate varied from 14.5% (95% CI 13.9–15.1) in women 50–54 years old to 43.4% (95% CI 39.0–48.1) in men 60–64 years old. FIT positivity rate directly correlated with age and gender, with relative risk increasing with older age and male gender.
- CRC detection rate decreased with each screening round and was associated with increasing age (relative risk for 5 year increase 1.45, 95% CI 1.35–1.56) and male gender (relative risk for women 0.51, 95% CI 0.44–0.59). First round CRC detection rate was 3.34% and 1.69% at the second round (relative risk 0.48, 95% CI 0.20–0.32), and 1% at subsequent rounds.
- Advanced adenoma detection rate significantly reduced from the first round at 15.9% to 8.5% (relative risk 0.51, 95% CI 0.47–0.56) at the second round and was also similarly associated with age and gender.

**LIMITATIONS:**

- The exclusion criteria limited the data collection to FITs performed in subjects who had repeated the tests as scheduled. This rejected 31,393 tests which would have increased FIT positivity rate and the CRC and advanced adenoma rate detection rates.
- Additional exclusion criteria underestimated the results from the 60 to 64-year-old age group as not

all were eligible for completing all the FITs as they aged.

- Chosen cut-off for test positivity and 2-year test interval which can limit generalization for FIT programs.
- Detection rates of CRC and advanced adenomas were used as surrogates for cancer prevention.
- Study was completed in north-east Italy. The results may not be generalizable to all screening populations.
- There is no direct comparison group for individuals undergoing primary endoscopy/colonoscopy screening although data from this study was compared to other studies with similar populations.
- "In the present FIT-based screening programme for 50 to 64-year-olds, the cumulative detection rates for CRC (0.85%) and advanced adenoma (5.9%) were similar with those reported for both an Italian primary colonoscopy screening (in subjects 50–69 years old: CRC 0.8%; advanced adenoma 6.0%) and in a US trial (subjects 50–84 years old: CRC 0.7%; advanced adenomas or sessile serrated polyps measuring ≥1cm 7.6%)."
- Higher chance of unmeasured confounders given the retrospective nature of the study.

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